frequency of sleep disturbance at baseline, among participants with or at risk for radiographic knee OA (ROA), and to estimate the association between the presence of inflammation on knee MRI and pain that disturbs sleep among knees that developed ROA.

Methods: Knees from the Osteoarthritis Initiative (OAI) with or at risk for ROA were included in this longitudinal analysis. Self-reported frequency of restless sleep in the past week was assessed using a CES-D question. Knee symptoms were assessed annually using the WOMAC. Knees that developed incident ROA (i.e., ≥2 Kellgren-Lawrence grade, KLG) through four years of follow-up were assessed for effusion-synovitis on non-contrast-enhanced 3T MRI using the MRI Osteoarthritis Knee Score (MOAKS) from annual clinic visits between four years prior to incident ROA and up to one year after ROA detection. Effusion-synovitis represents a combination of joint effusion and synovial thickening on fluid-sensitive sequences and scored as 0 (normal), 1 (mild), 2 (moderate), or 3 (severe). Annual mean WOMAC total score was estimated using a mixed model with participant and knee treated as random effects, in 5,028 knees at risk for ROA at baseline, and in 3,893 knees with ROA at baseline. Log-binomial regression with generalized estimating equations was used to estimate the association between effusion-synovitis and knee pain in bed that disturbs sleep, adjusted for age, sex, and BMI in a sample of 355 knees with an average of 3.8 MRI assessments.

Results: There was dose-dependent effect, with participants reporting restless sleep 1–2 days, 3–4 days, and 5–7 days in the past week having higher mean WOMAC total scores compared to those who reported <1 day of restless sleep (i.e., difference in means: 2.5 [95% CI: 1.3 to 3.8], 5.1 [95% CI: 3.2 to 7.1], and 10.1 [95% CI: 7.6 to 12.6], respectively) among knees with ROA (KLG≥2) at baseline. Differences in average WOMAC total score between groups were relatively persistent over nine years (Figure 1). A similar dose-dependent effect of restless sleep was observed among knees at risk of ROA (i.e., KLG 0 or 1). Among knees that developed incident ROA, those with mild effusion-synovitis had a 52% higher risk of knee pain in bed that disturbs sleep at the same visit (RR=1.52; 95% CI: 1.13 to 2.04), while knees that had moderate/severe effusion-synovitis had more than double the risk of knee pain that disturbs sleep (RR=2.55; 95% CI: 1.87 to 3.47), compared to knees with no MRI-detected effusion-synovitis.

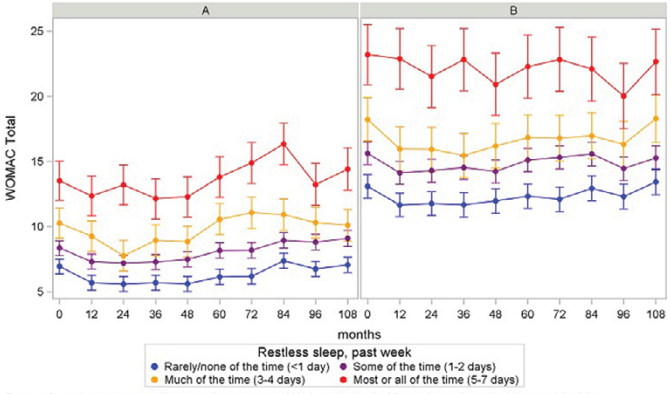

Figure 1. Sleep disturbance at baseline and estimated mean WOMAC total score with 95% confidence interval at follow-up clinic visits
A. Knees at risk for radiographic knee OA at baseline (KLG 0 or 1), B. Knees with radiographic knee OA at baseline (KLG 2+)

Conclusions: Restless sleep was associated with knee symptoms and disability in a dose-dependent manner, with average levels persistent over nine years of follow-up among knees with and at risk of ROA. Effusion-synovitis was associated with pain that disturbs sleep among knees that developed incident ROA. Sleep disturbance and knee inflammation may be important targets for interventions in knee osteoarthritis.

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SAT0501 PREVALENCE OF HAND OSTEOARTHRITIS IN A MODEL OF AUTO-IMMUNE DISEASE, SJÖGREN SYNDROME: RESULTS OF A PROSPECTIVE STUDY

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Background: Despite the role of chronic low-grade inflammation in osteoarthritis (OA), prevalence of OA during inflammatory or auto-immune diseases remains poorly assessed. A single study without a valid control group [1] and daily practice suggest an increased frequency of hand OA (HOA) in primary Sjögren Syndrome (pSS).

Objectives: We aimed investigate the prevalence of radiographic, symptomatic or erosive HOA in pSS and to compare these results with age and sex-matched control population suffering from dry eyes and mouth without auto-immune manifestation (sicca patients).

Methods: We included women with pSS fulfilling 2002 AECG European-American criteria and control women suffering from sicca symptoms without autoimunity who underwent a multidisciplinary day hospital. Standardized radiographs of hands were performed and were all read by an experimented reader. Radiographic HOA was defined as Kellgren-Lawrence score ≥2 on at least one joint. Erosive HOA was defined using the Verbruggen scoring system (phase E, subchondral erosion or R, remodelling of subchondral plate). Symptomatic HOA was defined as radiographic HOA associated with spontaneous hand joint pain and/or with a FIHOA ≥5 at the time of radiographs. We compared pSS versus sicca patients, pSS with radiographic HOA (pSS+, HOA+) versus pSS without radiographic HOA (pSS+, HOA-), and finally pSS with radiographic HOA (pSS+, HOA+) versus sicca patients with radiographic HOA (pSS-, HOA+).

Results: We included 34 patients with pSS (median age [range] 54.5 [28–84] years) and 54 patients with only sicca symptoms (57 [24–85] years). Among pSS patients, 41% had radiographic HOA, 12% had symptomatic HOA and 9% had erosive HOA. These prevalences did not differ from sicca patients (52% radiographic HOA p=0.45, 28% symptomatic HOA p=0.11, 9% erosive HOA p=1.0). The trend for a higher prevalence of symptomatic HOA in sicca patients compared to pSS is expected since these patients frequently suffer from dryness associated with fibromyalgia. In pSS patients, radiographic HOA was associated with a higher average age (pSS+HOA+:63,5 versus pSS+HOA-: 48,5 years old, p<0,01), with menopause (pSS+HOA+: 100% versus pSS+HOA-: 45%, p<0,01) and hypothyroidism (pSS+HOA+: 64% versus pSS+HOA-: 25%, p=0.04). There was no pSS feature such as autoantibodies profile or pSS disease activity, associated with radiographic or symptomatic HOA. Finally, HOA symptoms did not differ between patients with pSS and sicca symptoms. The prevalence of radiographic and erosive HOA in pSS and non-autoimmune sicca group seems in the same range as that observed in women from Framingham's cohort (44% and 10% respectively). And prevalence of symptomatic HOA seems similar in the pSS (12%) and in women from Framingham's cohort (16%).

Conclusions: The prevalence of HOA is not increased in pSS, a model of auto-immune diseases. Patients with pSS have the same HOA risk factors than in general population (age and menopause) and also hypothyroidism that may be involved in OA pathophysiology.

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SAT0502 A RANDOMIZED, PLACEBO-CONTROLLED, PROOF-OF-CONCEPT EFFICACY STUDY OF A MICROSOMAL PROSTAGLANDIN E SYNTHASE-1 (MPGES1) INHIBITOR AND A PROSTAGLANDIN E RECEPTOR (EP4) ANTAGONIST IN THE TREATMENT OF CANINE OSTEOARTHRITIS PAIN

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Background: Inflammation is a known contributor to osteoarthritis (OA) pain in animals and humans. While translation of human treatments to companion dogs is common, translation from companion dogs to humans is less frequent. We present results of a clinical study, in client-owned canines with moderate OA pain, which evaluated the efficacy of 2 molecules targeting the actions of prostaglandin E, either by modulating its production (mPGES1 inhibitor; LYA), or subsequent pharmacology through 1 of its 4 receptors (EP4 antagonist, LYB).

Objectives: To provide translational and comparative data to inform the potential utility of each of these mechanisms for treatment of chronic OA pain in humans and dogs.

Methods: A multicenter, randomized, double-blind, placebo (PBO)- and active-controlled trial in client-owned canine patients with moderate OA pain in ≥1 hindlimb/forelimb joint. Dogs ≥2 years of age with Liverpool Osteoarthritis in Dogs (LOAD) Mobility total score ≥13 to <46 were randomized (1:1:1:1) to 2 weeks of LYA (1.5 mg/kg/day), LYB (25 mg/kg/day), carprofen (4.4 mg/kg/day), or PBO. Efficacy versus PBO was assessed by mean change from baseline (CFB) to Week 2 in the Canine Brief Pain Inventory (CBPI) Pain Interference (PI) Score (primary endpoint), and for secondary endpoints: CBPI Pain Severity (PS) and Overall Impression (OI) subscores, and LOAD Mobility score. Data were analyzed by mixed-effect model for repeated measures with treatment, time, and interaction of treatment and time as fixed effects, and with baseline score, site, and weight as covariates. Posterior probability of treatments being superior to PBO was calculated with Bayesian methods.

Results: Of 163 dogs randomized, 158 (96.9%) completed the study. Treatment arms were well-balanced for baseline characteristics (mean [standard deviation] age: 9.3 [3.0] years, weight: 54.6% 15–32 kg, 45.4% >32–50 kg, CBPI PI: 5.1 [2.1]; CBPI PS: 4.2 [1.9]; LOAD Mobility: 24.1 [5.6]). Improvements (CFB) in CBPI PI were observed in all treatment groups after 2 weeks (Table). For LYA,

the probablility of superiority to PBO was 80% for CBPI PI and 89% to 96% for secondary endpoints. LYB showed inconsistent separation from PBO across the endpoints, with probablilty of superiority to PBO 54% to 89%. The separation of carprofen and PBO arms demonstrated assay sensitivity. The incidence of adverse events for LYA (35.9%) was comparable to that of carprofen (25.6%) and PBO (32.6%). For LYB, the incidence was significantly higher versus PBO (59.5%, P=.017).

Mean CFB to Week 2 in primary and secondary efficacy endpoints and probability of being superior to PBO

	LYA (n=39)	LYB (n=42)	Carprofen (n=39)	PBO (n=43)
CBPI PI (Primary)				
LS mean CFB (95% CI)	-1.85 (-2.44, -1.25)	-1.54 (-2.14, -0.95)	-2.12 (-2.73, -1.52)	-1.50 (-2.07, -0.92)
Prob. superior to PBO, %	80	54	93	
CBPI PS				
LS mean CFB (95% CI)	-1.66 (-2.14, -1.18)	-1.39 (-1.87, -0.91)	-1.56 (-2.05, -1.08)	-1.14 (-1.60,-0.68)
Prob. superior to PBO, %	94	78	90	
CBPI OI				
LS mean CFB (95% CI)	0.56 (0.30, 0.82)	0.37 (0.11, 0.63)	0.61 (0.35, 0.87)	0.35 (0.10, 0.59)
Prob. superior to PBO, %	89	56	93	
LOAD Mobility				
LS mean CFB (95% CI)	-6.18 (-8.38, -3.97)	-5.43 (-7.61, -3.24)	-7.52 (-9.75, -5.28)	-3.55 (-5.68, -1.42)
Prob. superior to PBO, %	96	89	99	

CI=confidence interval; LS=Least squares; Prob.=probability

Conclusions: The study results support an efficacy proof-of-concept signal for the mPGES1 inhibitor mechanism for treatment of chronic OA pain in canine patients.

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SAT0503 CAN BALNEOTHERAPY MODIFY MICRORNA EXPRESSION LEVELS IN OSTEOARTHRITIS? A COMPARATIVE STUDY IN PATIENTS WITH KNEE OSTEOARTHRITIS TREATED WITH MUD-BATH THERAPY

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Background: MicroRNAs (miRNAs) are a class of 19–23 nucleotides long non-coding RNAs that post-transcriptionally regulate the activity of target mRNAs. MicroRNAs are involved in cartilage homeostasis and play an important role in the pathogenesis of osteoarthritis (OA). They have been detected in human plasma and in synovial fluid and are considered as potential diagnostic biomarkers and therapeutic targets of OA. Balneotherapy is a common non-pharmacological treatment for OA patients. In a previous published prospective single-blind randomized clinical trial in patients with knee OA, we showed that a cycle of mud-bath therapy (MBT) in addition to conventional treatments induced an improvement on pain, functional capacity and quality of life in comparison to standard treatment alone.

Objectives: as part of this study we evaluated the whole blood levels of miR-155, 223, 181a, 146a and miR-let-7e, which are involved in the pathogenesis of OA.

Methods: Thirty-two patients aged between 50 and 75 years with knee OA defined by the ACR criteria were included for the current analysis, based on the availability of blood sample at basal time and after 2 weeks. Twenty-one patients (MBT group) were daily treated with a combination of daily local mud-packs at 42°C and baths in mineral water, at 37°C for 15 min, for a total of 12 applications over a period of 2 weeks, in addition to standard therapy; the other eleven patients (control group) continued their conventional treatment alone.

Clinical parameters [global pain score by a 0–100 mm Visual Analog Scale (VAS); physical function, total pain score and total stiffness score (WOMAC)] and microRNAs expression were performed at basal time and after 2 weeks. Peripheral whole blood was collected into PAXgeneTM Blood RNA tubes and then stored a -80°C. Total RNA was extracted using the PAXgeneTM Blood miRNA kit and the relative expression of miR-146a, miR-155, miR-223, miR-181a and miR-let-7e were determined by qRT-PCR.

Results: At the end of MBT we observed a statistically significant improvement of clinical paramethers. Furthermore, we observed a significant decrease of miR-155, 181a and miR-146a ($p<0.001$) and of miR-223 ($p<0.01$) expression levels. On the contrary, no clinical and biochemical modifications were detected in the control group. Concerning miR-let-7e expression levels no significant variations were showed in both groups after 2 weeks.

Conclusions: Our data showed that MBT can modify the expression levels of miR-155, 181a, 146a and 223 expression levels, that are up-regulated in OA. This MBT effect could be explained considering the role of the heat stress and of the hydrostatic pressure, since some miRNAs were found to be temperature and mechano-responsive. Further studies are needed to better explain the mechanism of action of MBT and the role of miRNAs in OA.

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SAT0504 PREDICTIVE ABILITY OF BIOMARKERS LINKED WITH SYNOVITIS FOR FUTURE INCIDENCE OF PAINFUL KNEE OSTEOARTHRITIS IN A COMMUNITY BASED COHORT OF MIDDLE-AGE WOMEN

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Background: Radiographic knee osteoarthritis (RKOA) is associated with the knee pain. However, more than half of the middle-aged individuals with RKOA will report no concurrent knee pain. Specific matrix metalloproteinases (MMPs) generated protein fragments have been associated with knee synovitis and suggested as specific neo-epitope biomarkers of joint remodelling.

Objectives: The aim of the study was to evaluate the association between MMP-derived neo-epitope biomarkers measured in serum, and future incidence of either painful RKOA or RKOA without pain, in a cohort of middle-aged women with no RKOA at baseline.

Methods: 585 participants (mean age 53.2, mean BMI 25.1) from the Chingford 1000 Women Study Chingford Women Study had serum biomarker levels of MMP- degraded of CRP (CRPM), collagen type II (C2M) and collagen type III (C3M) measured at year 2 or 3 of the study. All participants had a Kellgren Lawrence (KL) score of 0 in both knees at baseline. Ten years following the recruitment, incidence of RKOA was determined as KL $\geq$2 and painful RKOA was defined as the presence of pain on any number of days in the preceding month in the knee with RKOA. Log-transformed normalised biomarker levels were utilised in separate logistic regression models adjusted for age. Outcomes were defined as either RKOA without pain or painful RKOA. Further analyses were performed adjusting for both age and BMI.

Results: 24.6% of women developed RKOA during 10 years after the recruitment, but only 8.9% of developed RKOA associated with concurrent knee pain. After adjusting for age, statistically significant positive associations were found between C3M and CRPM and the risk of developing painful RKOA with odds ratio (OR) =3.4 (95% confidence interval (CI): 1.4 to 8.2), and OR=2.5 (95% CI: 1.2, 5.2) respectively. After adjusting for age and BMI, only C3M was positively associated with risk of developing painful RKOA with OR=3.2 (95% CI: 1.3, 7.8).

Conclusions: In a population of middle-aged women without knee osteoarthritis, an MMP generated neo-epitope of collagen III previously linked with knee synovitis (C3M) can independently identify high-risk individuals for developing painful RKOA. These findings indicate that targeting MMP activity may be a promising therapeutic strategy in well-targeted populations.

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SAT0505 SELF-REPORTED KNEE INSTABILITY ASSOCIATED WITH PAIN AND ACTIVITY LIMITATIONS PRIOR AND ONE YEAR AFTER TOTAL KNEE ARTHROPLASTY IN PATIENTS WITH KNEE OSTEOARTHRITIS

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Background: Sixty to 80% of the patients with knee osteoarthritis (OA) reported self-reported knee joint instability, which was associated with pain and activity limitations. One previous randomized control trial described the prevalence of retained self-reported knee joint instability after total knee arthroplasty (TKA) (32%). To better understand self-reported knee joint instability in usual care there is a need to replicate and extend the results.

Objectives: The aims of the study were to determine (i) the prevalence of self-reported knee instability prior and one year after TKA, (ii) the associations between self-reported knee instability, pain, activity limitations and quality of life prior and one year after TKA, (iii) the course of self-reported knee instability over time and (iv) the associations between retained knee instability, pain, activity limitations and quality of life.